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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/464,414	12/16/99	THANAVALA	Y	RPP:156CUS

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1651	9

DATE MAILED: 10/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/464,414	Thanavala
Examiner	**Group Art Unit**
Michele Flood	1651

☒ Responsive to communication(s) filed on *Jul 17, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-19* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-19* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on July 17, 2000.

The rejections made under 35 U.S.C. 112, second paragraph, have been overcome by Applicant's amendment of the claims.

The rejection of Claim 1 made under 35 U.S.C. 103(a) as being unpatentable over Koprowski et al. in view of Stites et al. has been overcome by Applicant's amendment.

The rejection of Claims 1-2 made under 35 U.S.C. 103(a) as being unpatentable over Arntzen et al. in view of Stites et al. has been overcome by Applicant's amendment.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of providing a secondary immune response in a mammal to the non-enteric pathogen antigen (NEPA), hepatitis B surface antigen (HBsAg), which is induced by the oral administration of genetically altered plant material of the family *Solanaceae* expressing the HBsAg, does not reasonably provide enablement for providing a secondary immune response to a non-enteric pathogen selected from the group consisting of pathogens which cause the infectious diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever.

The claims are drawn to a method for providing a secondary immune response in a mammal and/or a human comprising the oral administration of a substance comprising physiologically acceptable genetically altered plant material of the *Solanaceae* which expresses a NEPA, wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those pathogens which cause the infectious diseases hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever. The claims are further drawn to therapeutic regimen thereof, comprising feeding the mammal/and or human a genetically altered potato from the family *Solanaceae*.

The specification broadly discloses non-enteric pathogens that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin, e.g. blood transfusions

which can be used as sources of NEPA to raise a protective enteric immune response in mammals. However, the specification does not provide sufficient guidance as to how one of ordinary skill in the art would provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. The specification does not disclose other specific non-enteric pathogen antigens which have been subjected to the claim-designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. In regard to Claim 1, the specification other than the mere suggestion on page 1, lines 13-16 does not provide guidance as to how to use the instantly claimed invention to provide a secondary response to any (and) all diseases caused by a non-enteric pathogen that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin. Moreover, there is inadequate guidance as to how one of ordinary skill in the art would use the instantly claimed invention to genetically altered plant material to express any and all non-enteric pathogens other than HBsAg.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatment. The standard of enablement is higher for such inventions because effective treatments for providing immunological responses to the instantly disclosed pathogens are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to compositions intended for

the administration of compounds to humans generally require supporting evidence which clearly define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, applicant would have to demonstrate the functional effect and describe the effective amounts of each ingredient for the administration of the composition intended for a therapeutic treatment. Accordingly, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed plant materials expressing a non-enteric pathogen selected from those pathogens which cause the diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is made confusing by the phrase "in a mammal that is specific to an antigen". For clarity, "that is " should be replaced with to a and "to an" should be deleted.

The term "enteric immune response" in line 3 of Claim 1 renders the claim vague and indefinite because it is unclear as to the meaning of the term. Applicant may overcome the rejection by deleting the word "enteric" the term "enteric immune response" is not an art recognized term.

The word "immunizing" in lines 6 and 11 of Claim 1 makes the claim indefinite. Perhaps, Applicant can overcome the rejection by replacing "immunizing" with immunization.

Claims 1 and 2 are generally narrative and indefinite, failing to conform with current U.S. practice. The claims are so replete with grammatical and idiomatic errors that they are too numerous to be listed separately; and, thus they are incomprehensible. These claims should be appropriately amended.

Regarding Claim 3, there is an apparent misspelling in line 3 "staphylococcus aureous". Applicant may overcome the rejection by replacing "staphylococcus aureous" with *Staphylococcus aureus*.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koprowski et al. (A) in view of Stites et al. (U).

The claims are directed to providing a secondary immune response in a mammal and/or a human that is specific to a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in a mammals free of acquired immunity to the pathogen, the method comprising rendering the mammal immunoreceptive to the NEPA by prior immunizing against a non-enteric pathogen containing the NEPA by vaccination followed by feeding the immunoreceptive mammal with a substance comprising a physiologically acceptable material containing the NEPA from a transgenic plant expressing the NEPA to cause a secondary immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA in the absence of prior immunizing. The claims are further directed to a method wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever. The claims are further directed to a therapeutic regimen thereof, comprising feeding the mammal/and or human a genetically altered potato from the family *Solanaceae*.

Applicant argues that the reference of Koprowski does not teach a the feeding of a transgenic plant expressing a non-enteric pathogen, however, this is not persuasive because Koprowski teaches a method of providing an immune response in a mammal and/or human to a non-enteric pathogen, especially the non-enteric pathogen rabies street virus. In the process, a physiologically acceptable plant is genetically altered to express an antigen. See Claim 4, in Column 23. The transgenic plant material is used as an oral delivery system to feed an individual a non-enteric pathogen antigen. Routes of administration in the delivery of the substance comprising the plant material containing the NEPA are taught in Column 5, lines 43-61. In Column 7, lines 18-31, Koprowski teaches other viral, fungal, and bacterial pathogens which can be used against the invention. Koprowski teaches, in Column 8, lines 24-31, plant-infecting microorganisms and solanaceous plants hosts, including potatoes. Applicant further argues that the teachings of Koprowski demonstrate only the feeding of plant material expressing a gene for rabies N protein, and that since rabies is known to have the ability to invade a mammal by means other than through a breach in the skin and can raise an immune response without an adjuvant or prior immunization, the referenced method does not meet the criteria for non-enteric pathogens in the claims. However, the use of an adjuvant is not commensurate with the claimed subject matter. Furthermore, the examiner notes that the Markush group of Claim 3 includes *Staphylococcus aureus* and it is known in the art that staphylococcal infections may be acquired by an individual via enteric transmission, for example, the contamination of food products by feces containing the

bacteria. Moreover, Hirsh teaches that most rabies cases are caused by the bite of a rabid animal; and, that only in exceptional circumstances, rabies may be acquired by inhaling aerosol containing rabies virus in bat caves or by virus passing through intact mucous membranes. Furthermore, at the time the invention was made the art taught that the exposure of an individual to the rabies virus did not raise a protective immune response because Hirsh teaches that while [T]the cellular and humoral immune responses are important in preventing rabies by vaccination but so far have not been found to function in recovery from rabies infections. See page 414, Column 2, lines 38-42. Applicant also argues that Koprowski does not disclose or suggest making a mammal immunoreceptive by prior vaccination as required by the present claims. However, in the absence of distinguishing the definition of the term "immunoreceptive" over the prior art, even in view of the instant claims, specification, and Applicant's arguments, this is not persuasive because Koprowski clearly teaches the ingestion of transgenic plant material expressing a non-enteric pathogen antigen wherein the oral administration of the plant material substance as an oral vaccine delivery system elicits an immune response specific to the non-enteric pathogen antigen which is greater than the immune response to the non-enteric pathogen antigen prior to the immunization method. See Figures 14 and 15, wherein Koprowski demonstrates an IgG antibody serum response specific to rabies nucleoprotein. Moreover, Koprowski teaches a method of providing protective immunity to an individual by the administration of the vaccine by both and intravenous injections and ingestion of the plant material. Koprowski does not expressly teach a method for

providing a secondary immune response to a non-enteric pathogen; and, although Applicant would argue that Stites does not teach oral vaccines or the administration of an oral vaccine against a NEPA in the presence of a suitable adjuvant, this is not commensurate with the claimed subject matter. The secondary reference of Stites was relied upon because Stites teaches the principles of immunization which may be applied to a variety of vaccine types. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a secondary immune response to a non-enteric pathogen in a mammal and/or human which was made "immunoreceptive" by vaccination by feeding the individual transgenic plant material expressing a non-enteric pathogen antigen because Stites teaches on page 724, Column 2, lines 1-42, the principles of "booster" reimmunization in a previously immune or "immunoreceptive" individual. One would have been motivated to optimize the teachings of Koprowski by inducing a secondary immune response in an individual wherein the individual ingests genetically altered plant material expressing a non-enteric pathogen antigen, such as a solanaceous potato, because Stites teaches that reimmunization or a "booster shot" in a previously immune individual provides a rapid secondary increase in immunity. One would have had a reasonable expectation of success because Stites teaches that the timing of immunization, the interval between doses, and the timing of booster reimmunization are based on both theoretic considerations and vaccine trials.

As the references indicate the various ingredients, various proportions, and various times for the administration of a vaccine, they would be routinely optimized by one of ordinary skill in the art practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

6. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arntzen et al. (B) and Koprowski et al. (A), and further in view of Stites et al. (U).

The claims are directed to providing a secondary immune response in a mammal and/or a human that is specific to a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in a mammals free of acquired immunity to the pathogen, the method comprising rendering the mammal immunoreceptive to the NEPA by prior immunizing against a non-enteric pathogen containing the NEPA by vaccination followed by feeding the immunoreceptive mammal with a substance comprising a physiologically acceptable material containing the NEPA from a transgenic plant expressing the NEPA to cause a secondary immune response to oral administration specific to the NEPA stronger that a response specific to NEPA caused by the NEPA in the absence of prior immunizing. The claims are further directed to a method wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever,

tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever. The claims are further directed to a therapeutic regimen thereof, comprising feeding the mammal/and or human a genetically altered potato from the family *Solanaceae*.

Applicant argues that the method of Arntzen does not teach the ingestion of a tomato or a potato plant expressing HBsAg would cause an immune response to HBsAg and that Arntzen provides no supporting data showing an immune response due to the ingestion of the plant material, such as tomato juice. Applicant further argues that to the extent that Arntzen teaches that tomato juice or any other plant material containing HBsAg can be used as a vaccine, it is an inoperative reference since there is no teaching or suggestion as to how that might be done; and, that "Simply ingesting the plant material, as suggested by Arntzen does not confer immunity. This is neither commensurate with the instantly claimed subject matter nor is it persuasive because Arntzen clearly teaches an anti-viral vaccine produced in physiologically acceptable plants, particularly the potato and the tomato, and then administered through standard vaccine procedure or by feeding the plants to an animal or a human. Arntzen specifically teaches methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material. Arntzen also teaches methods of making a vaccine by recovering the immunogen expressed in the plant cell for use as a vaccine. Moreover, Arntzen expressly teaches that the physiologically acceptable plant materials expressing the HBsAg can be used both to prime the

mucosal immune system and/or stimulate the humoral immune response in a dose dependent manner. See Column 3, lines 24, Columns 4-7 and Column 8, lines 1-21. In Column 11, lines 36-50, Arntzen teaches that either the parenteral or non-parenteral introduction of the vaccine to a mammal can elicit serum and/or secretory antibodies against the HBsAg immunogen of the vaccine with minimal induction of systemic tolerance. Finally, Arntzen teaches that a plurality of different administrations of the genetically altered plant material expressing HBsAg over separate periods of time will provide the claimed functional effect of raising the serum IgM and IgG response specific to the hepatitis B surface antigen to achieve a secondary immune response or immunization of a mammal. Note that Arntzen specifically teaches that the plurality of times for the administration of the vaccines is in a range of 3 to 6, and that the time separating the vaccinations is in a range of 14 to 35 days to achieve protective levels of antibodies. See Column 15, lines 45-61. Therefore, the reference of Arntzen clearly teaches a method of providing a secondary immune response. Arntzen does not expressly teach plant material from the *Solanaceae* family, however the teachings of Koprowski as taught above teaches plant infecting microorganisms and solanaceous plants, including potatoes used to express non-enteric pathogens. Therefore, it would have been obvious to one of ordinary skill in the art to replace the plant material which was not physiologically acceptable to mammals and/or humans, i.e. tobacco, taught by Arntzen with the solanaceous plants taught in the method of Koprowski because one would have been motivated and had a reasonable expectation that the modification of the method

for providing a transgenic plant expressing a non-enteric pathogen antigen used in a method for providing a secondary immune response via the administration of plant substance as an oral vaccine delivery system would be physiologically acceptable to mammals and/or humans. Applicant further argues that Stites does not teach oral vaccines or the administration of an oral vaccine against a NEPA in the presence of a suitable adjuvant, however, this is not commensurate with the claimed subject matter. The secondary reference of Stites was relied upon because Stites teaches the principles of immunization which may be applied to a variety of vaccine types. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a secondary immune response to a non-enteric pathogen in a mammal and/or human which was made "immunoreceptive" by vaccination by feeding the individual transgenic plant material expressing a non-enteric pathogen antigen because Stites teaches on page 724, Column 2, lines 1-42, the principles of "booster" reimmunization in a previously immune or "immunoreceptive" individual. One would have been motivated to optimize the teachings of either Koprowski or Arntzen by inducing a secondary immune response in an individual wherein the individual ingests genetically altered plant material expressing a non-enteric pathogen antigen, such as a solanaceous potato, because Stites teaches that reimmunization or a "booster shot" in a previously immune individual provides a rapid secondary increase in immunity. One would have had a reasonable expectation of success because Stites teaches that the timing of immunization,

the interval between doses, and the timing of booster reimmunization are based on both theoretic considerations and vaccine trials.

As the references indicate the various ingredients, various proportions, and various times for the administration of a vaccine, they would be routinely optimized by one of ordinary skill in the art practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Michael Wityshyn whose telephone number is (703) 308-4743.

LEON B. LANKFORD, JR.
PRIMARY EXAMINER

mcf

September 27, 2000